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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,915	03/12/2007	David Wallach	30694/41943	5262

4743 7590 05/13/2008

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
05/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,915	WALLACH ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,7-11,13-24,26-31,33-43,45-47 and 49-62* is/are pending in the application.

4a) Of the above claim(s) *5,7-11,13-24,26-31,33-43,45-47 and 49-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims 1-7 and of the antisense polynucleotide as the species of active agent and acute myelogenous leukemia as the disease in the reply filed on 02/22/2008 is acknowledged. Applicant also cancelled claims 1, 4, 6, 12, 25, 32, 44, and 48 and amended claims 2, 5, 9-10, 13-14, 16-17, 24, 26-27, 29-31, 33-34, 36-37, 41-42, 45-46, 49-50, 52-53, 56-57, 60 and 62. The traversal is on the grounds that, in view of the amendments, Applicant submits that the claims share a common technical feature and exhibit a single general inventive concept. This is not found persuasive because as iterated in the election /restriction requirement sent on 01/22/2008, the claims, as originally filed, lacked unity because inhibitors of Caspase-8 and therapeutical methods of use for them were known in the art as evidenced by Golec et al. (WO/01/10383, 02/15/2001).

The requirement is still deemed proper and is therefore made FINAL.

Status of the claims

2. Claims 2, 3, 5, 7-11, 13-24, 26-31, 33-43, 45-47, and 49-62 are pending. Claims 5, 7-11, 13-24, 26-31, 33-43, 45-47 and 49-62 are withdrawn as being drawn to non-elected subject matter. Claims 2 and 3 are under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting hematopoiesis by down regulating the expression of caspase 8 with particular antisense oligonucleotides (a for instance the sequences used by Zhang et al., see infra), does not reasonably provide enablement for a specific untested antisense sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claim is drawn to a method of inhibiting hematopoiesis in a subject comprising down regulating an expression or activity of caspase-8 by an antisense polynucleotide capable of specifically hybridizing with an mRNA transcript encoding caspase-8 having the sequence of Seq. Id. No.: 16.

The field of inhibition of protein expression and/or activity by using antisense oligonucleotides is advanced but however unpredictable (see for instance Ulanova et al., BioDrugs, 20, 1-11, 2006). The critical issues are the selection of the target and the specificity of the binding of the oligonucleotide to the target, the delivery of the oligonucleotide to a particular cell and the stability of the oligonucleotides once delivered to the cell. All these steps imply a considerable amount of experimentation. Even with the improvements noted in the art for issues like delivery and oligonucleotide stability, a remaining issue that is dealt with by experimentation only is target selection and specificity. Even if, by *in silico* methods, a person of ordinary skill in the art would have a number of sites in the mRNA of the molecule that is desired to be down regulated, it still needs a considerable amount of experimental validation. This is more acute in the case of the instant Application, in which no working examples are presented with respect to the use of any oligonucleotide for down regulating caspase-8. The guidance provided with respect to the effects of down regulating Caspase-8 refers to knocking out the gene in mice. From here, Applicant tries to infer that by using oligonucleotides of Seq. Id. No.: 16, one can achieve the same effect. By knocking out of a gene one would infer that the mRNA for the gene is not transcribed so that factors that are introduced when an antisense oligonucleotide is used (for instance non-specific binding, inefficient down regulation due to a poor choice of region to be bound) are not considered. For these reasons, it is considered that the use of an oligonucleotide of Seq. Id. No. 16 for down regulation of the expression of caspase-8 would entail an amount of experimentation that is considered undue. Therefore, only experimentally

tested antisense oligonucleotides but not the untested Seq. Id. No. 16 are commensurate in scope with the claims.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, it is not clear if there is only one oligonucleotide claimed in the method. By using "a" sequence instead of "the" sequence, one would not know if there are multiple sequences claimed (e.g. whether applicants intend the entirety of the sequence, or any fragment thereof) and the metes and bounds of the claim could not be established.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (U.S. Pub No. 20030083296, 05/01/2003).

The claims is drawn to a method of inhibiting hematopoiesis in a subject comprising downregulating an expression or activity of caspase-8 in the subject, wherein said downregulating said expression or activity of caspase-8 is effected by an antisense polynucleotide capable of specifically hybridizing with an mRNA transcript encoding caspase-8.

Zhang et al. teach compositions comprising antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding caspase 8 and methods of using these compounds for modulation of caspase 8 expressions and for treatment of diseases associated with expression of caspase 8 (abstract). The antisense compounds specifically hybridize with one or more nucleic acids encoding caspase 8 (DNA encoding caspase 8, RNA (including pre-mRNA and mRNA), transcribed from such DNA, and also cDNA derived from such RNA). The specific hybridization of an oligomeric compound with its target nucleic acid interferes with the normal function of the nucleic acid. This modulation of function of a target nucleic acid by compounds which specifically hybridize to it is generally referred to as "antisense". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with include all vital functions such as, for example, translocation of the RNA to the site of protein translation, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA. The overall effect of such interference with target nucleic acid function is modulation of the expression of caspase 8 ([0014]). One of the methods of treatment specifically names a hematopoietic disorder (claim 18).

Thus, claim 2 is anticipated by Zhang et al.

Conclusion

8. No claims are allowed. Seq. Id. No.:16 *if proved enabled*, is free of prior art and the closest prior art for the sequence is sequence 16 in Agami et al. (WO/03/056012, 07/10/2003) which is 50% identical with the Seq. Id. No.:16 of the instant Application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/Ph.D.
Primary Examiner, Art Unit 1647